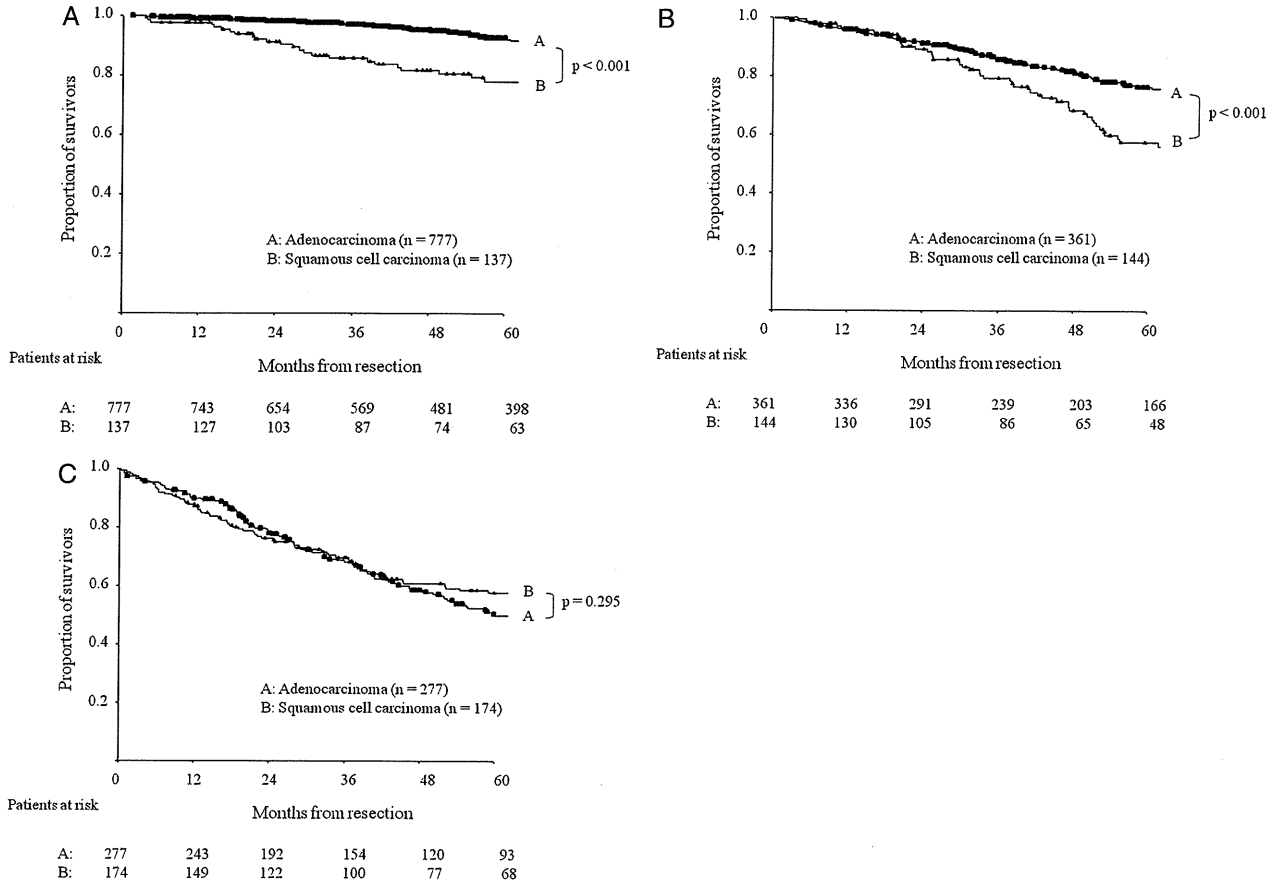

FIGURE 4. Overall survival curves according to histology in each stage. A, Overall survival curves in stage IA. B, Overall survival curves in stage IB. C, Overall survival curves in stage II.

and SCC (5-year overall survival rate: 79.7% and 63.8%, respectively) (Fig 2A), whereas no difference in recurrence-free probability was observed between adenocarcinoma and SCC (5-year recurrence-free probability: 78.4% and 76.0%, respectively) (Fig 2B). The causes of death for patients with adenocarcinoma and SCC are shown in Table 1. The cumulative hazard rate of other causes of death (Fig 3) for patients with SCC was significantly higher than those for patients with adenocarcinoma ($P < .001$).

Correlation Between Histology and Clinicopathologic Factors

The details of patient characteristics and histology are shown in Table 2. Among 1,415 patients with adenocarcinoma, 658 (47%) were never smokers and 757 (53%) were ever smokers. Four hundred fifty-five patients with SCC included 10 (2%) never smokers and 445 (98%) ever smokers. Ever smokers were more common in patients with SCC compared with those with adenocarcinoma. SCC was more common in older patients and male patients. In SCC, significantly more tumors exhibited larger tumor sizes, IVI, lymph node metastases, and stage IB or higher.

Overall Survival Rates and Recurrence-Free Probabilities for Patients With Adenocarcinoma and SCC According to Stage

Figures 4A-4C show the overall survival curves plotted according to the histology in stages IA, IB, and II. A statistically significant difference in the 5-year overall survival rate was observed between adenocarcinoma and SCC in stage IA (92.7% and 78.0%, respectively) (Fig 4A) and stage IB (76.5% and 57.6%, respectively) (Fig 4B), whereas no difference was observed in stage II (49.8% and 57.6%, respectively) (Fig 4C). Figures 5A-5C show the recurrence-free probability curves plotted according to the histology in stages IA, IB, and II. In stage IA, the 5-year recurrence-free probability for adenocarcinoma was significantly higher than that for SCC (91.4% and 82.6%, respectively) (Fig 5A). No difference was observed in stage IB (74.4% and 73.6%, respectively) (Fig 5B). In stage II, the 5-year recurrence-free probability for adenocarcinoma was significantly lower than that for SCC (46.5% and 72.5%, respectively) (Fig 5C).

Because of the significant differences in recurrence-free probability between patients with adenocarcinoma and SCC in stage IA and II, we examined

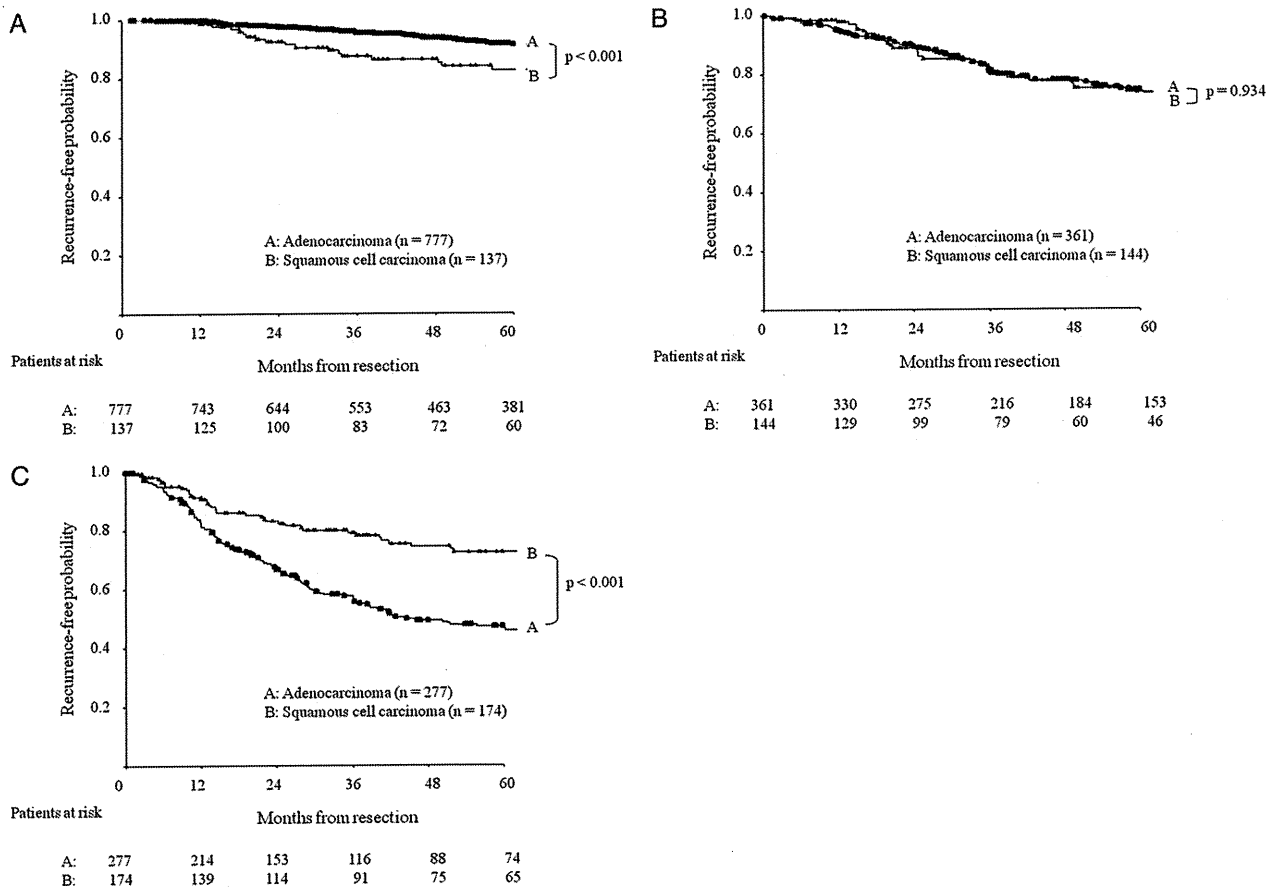

FIGURE 5. Recurrence-free probability curves according to histology in each stage. A, Recurrence-free probability curves in stage IA. B, Recurrence-free probability curves in stage IB. C, Recurrence-free probability curves in stage II.

whether histology could be an independent risk factor in stage IA and II. Table 3 lists 5-year recurrence-free probabilities according to clinicopathologic features of stage IA. Univariate analysis identified the following six statistically significant risk factors for recurrence: age, sex, smoking history, histology, lymphatic permeation, and IVI. In multivariate analysis, the presence of lymphatic permeation and IVI were found to be statistically significant independent risk factors for recurrence (Table 3). The correlation between histology and independent risk factors for recurrence of stage IA NSCLC is shown in Table 4. Patients with SCC showed significantly higher incidence of tumors with IVI (Table 4).

Table 5 lists the 5-year recurrence-free probabilities according to clinicopathologic features of stage II NSCLC. Univariate analysis identified the following five statistically significant risk factors for recurrence: histology, lymphatic permeation, IVI, VPI, and number of metastatic lymph nodes. In multivariate analysis, adenocarcinoma histology and presence of VPI were found to be statistically significant independent risk factors for recurrence (Table 5).

Recurrence-Free Probabilities for Never and Ever Smokers With Adenocarcinoma and Characteristics of Adenocarcinoma According to Stage

A statistically significant difference was observed in recurrence-free probability between never and ever smokers in patients with adenocarcinoma: 5-year recurrence-free probabilities of 82.2% and 74.9%, respectively (Fig 6). Never smokers were more common in stage IA (Table 6). In stage IA, significantly more tumors were found by CT screening and more patients with predominantly BAC subtype were more common compared with stage IB or higher (Table 6).

DISCUSSION

Among many prognostic factors for patients with lung cancer, histology is an easily available pathologic factor after tumor resection. Although most studies that generally compared adenocarcinoma to SCC have not shown histologic type to be an independent prognostic factor, some studies have concluded that adenocarcinoma favorably influences the prognosis

Table 3—*Univariate and Multivariate Analyses of Risk Factors for Recurrence in Stage IA*

Characteristic	No. Patients (%)	5-y Recurrence-Free Probability, %	Univariate *P* Value by Log-Rank Test	Multivariate Analysis		
				HR	95% CI	*P* Value
Overall	914	90.2	...	...	...	...
Age, y						
≤65	490 (54)	92.3	.034	1	...	...
>65	424 (46)	87.5	...	1.415	0.921-2.174	.113
Sex						
Women	445 (49)	93	.004	1	...	...
Men	469 (51)	87.4	...	1.021	0.534-1.950	.95
Smoking history						
Never smoker	409 (45)	92.7	.003	1	...	...
Ever smoker	505 (55)	88	...	1.09	0.553-2.149	.804
CEA						
Within normal range	702 (77)	91.2	.164	Not included in multivariable model		
Elevated	210 (23)	86.6	...			
Not examined	2	...	...			
Tumor laterality						
Right	588 (64)	91.3	.122	Not included in multivariable model		
Left	326 (36)	88.1	...			
Primary lobe						
Upper or middle lobe	612 (67)	90.5	.39	Not included in multivariable model		
Lower lobe	302 (33)	89.5	...			
Tumor size, cm						
≤2.0 (T1a)	519 (57)	91.2	.323	Not included in multivariable model		
>2.0 (T1b)	395 (43)	88.8	...			
Histologic type						
Adenocarcinoma	777 (85)	91.4	<.001	1	...	...
SCC	137 (15)	82.6	...	1.663	0.987-2.802	.056
Lymphatic permeation						
Absent	805 (88)	92.3	<.001	1	...	...
Present	109 (12)	77	...	1.985	1.240-3.179	.004
Intratumoral vascular invasion						
Absent	740 (81)	94	<.001	1	...	...
Present	174 (19)	74.4	...	3.629	2.307-5.708	<.001

HR = hazard ratio. See Tables 1 and 2 legends for definition of other abbreviations.

in early-stage NSCLC.[2,3] However, there are still several issues to be answered concerning histology: Is histology important as a recurrence risk factor in NSCLC after complete tumor resection? If so, in which stage? We investigated the relationships between histology and clinicopathologic characteristics and evaluated its significance as a predictor of recurrence.

Table 4—*Correlation Between Histology and Independent Risk Factors for Recurrence in Stage IA*

Characteristics	Histologic Type		*P* Value
	Adenocarcinoma	SCC	
Total, No.	777	137	...
Lymphatic permeation			
Absent	689 (89)	116 (85)	.198
Present	88 (11)	21 (15)	...
Intratumoral vascular invasion			
Absent	643 (83)	97 (71)	.002
Present	134 (17)	40 (29)	...

Values given as No. (%) unless otherwise noted. See Table 1 legend for expansion of abbreviation.

In the current study, significantly lower overall survival rate was observed in SCC, whereas no significant difference was observed in recurrence-free probability in the entire cohort. There were several clinicopathologic differences between patients with early-stage adenocarcinoma and SCC. SCC was more common in older patients and male patients. Ever smokers were more common in patients with SCC compared with those with adenocarcinoma. Cigarette smoking is a well-known risk factor for severe pulmonary and cardiovascular diseases.[10] Several studies[6,16-18] found that approximately 20% to 40% of smokers with lung cancer died without evidence of cancer progression or recurrence. Significantly more patients died of other diseases in ever smokers also in the current study, and more patients with SCC died of other diseases, which may partly explain the discrepancy between recurrence-free probability and overall survival rate in patients with early-stage NSCLC.

Table 5—*Univariate and Multivariate Analyses of Risk Factors for Recurrence in Stage II*

Characteristic	No. of Patients (%)	5-y Recurrence-Free Probability (%)	Univariate *P* Value by Log-Rank Test	Multivariate Analysis		
				HR	95% CI	*P* Value
Overall	451	56.1	...	...	...	...
Age, y						
≤65	203 (45)	56.7	.225	Not included in multivariable model		
>65	248 (55)	55.4	...			
Sex						
Women	117 (26)	50.7	.894	Not included in multivariable model		
Men	334 (74)	58.3	...			
Smoking history						
Never smoker	95 (21)	44	.094	Not included in multivariable model		
Ever smoker	356 (79)	59.8	...			
CEA						
Within normal range	245 (54)	56.3	.445	Not included in multivariable model		
Elevated	205 (45)	55.4	...			
Not examined	1					
Primary lobe						
Upper or middle lobe	248 (55)	59.6	.268	Not included in multivariable model		
Lower lobe	203 (45)	51.4	...			
Tumor size, cm						
≤5.0	280 (62)	54.3	.789	Not included in multivariable model		
>5.0	171 (38)	59.6	...			
Histologic type						
SCC	174 (39)	72.5	<.001	1	...	...
Adenocarcinoma	277 (61)	46.5	...	2.084	1.474-2.948	<.001
Lymphatic permeation						
Absent	267 (59)	63.5	.012	1	...	...
Present	184 (41)	47.3	...	1.3	0.959-1.762	.091
Intratumoral vascular invasion						
Absent	134 (30)	62.6	.019	1	...	...
Present	317 (70)	53.3	...	1.338	0.918-1.949	.13
Visceral pleural invasion						
Absent	240 (53)	62.9	.001	1	...	...
Present	211 (47)	48.4	...	1.488	1.087-2.037	.013
Intrapulmonary metastasis						
Absent	393 (87)	55.4	.942	Not included in multivariable model		
Present	58 (13)	59.1	...			
Number of metastatic N1 lymph nodes						
Absent or single	326 (72)	59.8	.023	1	...	...
Multiple	125 (28)	46.7	...	1.305	0.943-1.806	.108
Highest level of involved lymph node station						
Absent or peripheral (12-14)	336 (75)	56.3	.762	Not included in multivariable model		
Hilar (10) or interlobar (11)	115 (25)	55.3	...			

See Tables 1-3 legends for expansion of abbreviations.

Because significantly more tumors exhibited larger tumor sizes, and stage IB or higher in SCC, we evaluated the significance of histology as a predictor of recurrence in each stage. Both overall survival rate and recurrence-free probability of patients with SCC were significantly lower than those of patients with adenocarcinoma among patients with stage IA tumors. These results suggest that in patients with stage IA tumors, SCC is more aggressive than adenocarcinoma. On the basis of the results of multivariate analyses, the presence of lymphatic permeation and IVI were independent predictors of recurrence in stage IA. IVI has been reported to be a strong independent factor for a poor prognosis in pathologic stage I NSCLC also by several authors.[19-24] Although histology was not shown as an independent predictor of recurrence in stage IA, pathologic characteristics showed that SCC was significantly more frequently accompanied by IVI than adenocarcinoma. This invasive characteristic might be the reason for more frequent recurrence in patients with SCC than in patients with adenocarcinoma in stage IA.

In stage II, significantly lower recurrence-free probability was observed in adenocarcinoma, whereas no significant difference was observed in overall survival rate. In contrast to stage IA, this finding suggests that adenocarcinoma behaves more aggressively compared with SCC in stage II. In the current study,

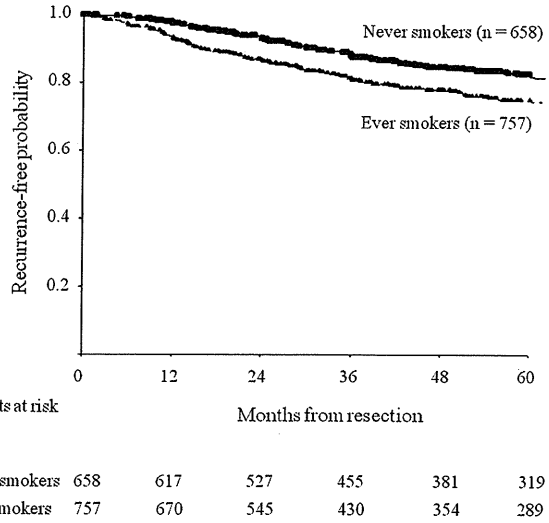

FIGURE 6. Recurrence-free probability curves of adenocarcinoma patients according to smoking history.

adenocarcinoma histology was one of the significant independent risk factors for recurrence in stage II, although adenocarcinoma favorably influenced the prognosis in stage IA. The significance of histology in postoperative outcome differs according to disease stage. Therefore, disease stages should be considered while evaluating histology as a predictor of recurrence after tumor resection.

Adenocarcinomas are typically very heterogeneous, showing a wide variety of histologic features, including BAC, acinar, papillary, and solid adenocarcinoma.[13] Among these major histologic subtypes, BAC is often reported to be associated with a favorable prognosis,[25-27] and the number of patients with BAC subtypes among never smokers has recently increased. In the current study, never smokers and patients with predominantly BAC subtype were more common in stage IA compared with stage IB or higher. Several authors reported that adenocarcinomas detected by CT screening showed a favorable postoperative prognosis and were correlated with BAC subtype.[28] Also in the current study, significantly more tumors were found by CT screening in stage IA, which suggests that there are different kinds of adenocarcinoma and that these are differently represented within the different substages. This may be the reason that the significance of histology in postoperative outcome differs according to disease stage.

The primary strength of this study is the large number of patients. However, this retrospective study had several limitations in the analyses. Because of the higher frequency of epidermal growth factor receptor gene mutations in patients with adenocarcinoma,[29,30] epidermal growth factor receptor inhibitors may be effective in possibly prolonging survival after recurrence, mostly in patients with adenocarcinoma with epidermal growth factor receptor mutations. In this study, we only focused on recurrence and failed to assess the outcomes between adenocarcinoma and SCC after recurrent diagnosis. This may influence the discrepancy between the overall survival rate and recurrence-free probability other than smoking-related comorbidities in stage II. Another limitation is the lack of ethnic diversity, because our patient population was 100% Japanese. Despite these limitations, our results clearly showed the stage in which histology had a prognostic impact after complete tumor resection.

CONCLUSION

Ever smokers were more common in patients with SCC, and significantly more patients with SCC died of other diseases. It is important to offset the prognostic impact of comorbidities associated with cigarette smoking for evaluating histology as a prognostic factor. No significant difference was observed in recurrence-free probability in the entire cohort, but significantly more tumors exhibited larger tumor sizes and stage IB or higher in SCC. When evaluating its

Table 6—*Characteristics of Adenocarcinoma According to Stage*

Characteristic	No. Patients (%)	Stage IA	Stage IB	*P* Value[a]	Stage II	*P* Value[a]
Total	1,415	777	361	...	277	...
Smoking history						
Never smoker	658 (47)	406 (52)	158 (44)	...	94 (34)	...
Ever smoker	757 (53)	371 (48)	203 (56)	.009	183 (66)	<.001
Method of tumor detection						
CT screening	619 (44)	433 (56)	114 (32)	...	72 (26)	...
Others	796 (56)	344 (44)	247 (68)	<.001	205 (74)	<.001
Predominant subtype						
BAC	737 (52)	520 (67)	130 (36)	...	87 (31)	...
Others	678 (48)	257 (33)	231 (64)	<.001	190 (69)	<.001

BAC = bronchioloalveolar carcinoma.
[a]Compared with stage IA.

significance as a predictor of recurrence stratified by stage, histology showed different impact on postoperative recurrence in patients with NSCLC within different substages. Histologic subtype distribution was different between stage IA and stage IB or higher in patients with adenocarcinoma. Disease stages should be considered while evaluating histology as a predictor of recurrence after tumor resection.

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Dr Yoshida: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Ishit: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Hishida: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Nishimura: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Nagai: contributed to the design and coordination of the study, revised the article for important intellectual content, and read and approved the final manuscript.
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Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

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Prognostic Significance of a Solid Component in Pulmonary Adenocarcinoma

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Background. We retrospectively analyzed pulmonary adenocarcinoma patient survival in our single-institution database to evaluate the impact of solid adenocarcinoma components (SAC) on survival and to propose a method of incorporating SAC into the T classification in future staging systems.

Methods. We reviewed 504 consecutive patients with surgically resected pulmonary adenocarcinoma for their clinicopathologic characteristics and prognoses, stratifying patients according to predominant adenocarcinoma subtype. We also stratified patients with an SAC-containing tumor according to the ratio of SAC in analyzing outcome.

Results. Patients with SAC (SAC+) had significantly poorer prognoses than patients without any SAC (SAC−), irrespective of SAC ratio. Patient groups stratified by pathologic T classification up to T2b could be divided into four categories according to SAC status in decreasing order of survival: (I) T1a/SAC−; (II) T1b/SAC−; (III) T1a/SAC+, T1b/SAC+, and T2a/SAC−; and (IV) T2a/SAC+ and T2b/SAC−.

Conclusions. Pulmonary adenocarcinoma patients with any amount of SAC had worse prognoses than those without any SAC. The presence of SAC was an independent unfavorable prognostic factor, comparable to other pathologic findings indicating invasion. Solid adenocarcinoma component was an upstaging factor in T classification for T1 and T2a pulmonary adenocarcinomas. If SAC is present, we propose T1 and T2a tumors should be classified as T2a and T2b, respectively.

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In Japan, adenocarcinoma is the most common histologic type of resected lung cancers, accounting for more than 60% of cases [1]. The major histologic subtypes of adenocarcinoma are bronchioloalveolar carcinoma (BAC), acinar adenocarcinoma, papillary adenocarcinoma, solid adenocarcinoma, and adenocarcinoma with mixed subtype. Adenocarcinoma with mixed subtype is the most frequent subtype and accounts for approximately 80% of resected adenocarcinomas [2].

Bronchioloalveolar carcinoma is the only subtype reported to be associated with a relatively favorable prognosis [3–5], whereas the other subtypes are considered as invasive components and associated with poor outcome [2, 4–8]. Histologically, solid adenocarcinoma is the less-differentiated subtype, but only a few studies have evaluated its invasiveness and prognostic impact independently of the other subtypes [9, 10].

In this retrospective study, we investigated the prognostic impact of the amount of solid adenocarcinoma component (SAC) in pulmonary adenocarcinoma patients.

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Patients and Methods

Patient Selection

From January 2003 through December 2005, 793 consecutive patients underwent surgical resection for primary non–small cell lung carcinoma at our hospital. After excluding 257 patients with nonadenocarcinomas, 18 with incomplete data, 11 with preoperative neoadjuvant chemoradiotherapy, and 3 with incomplete resection, the remaining 504 patients were enrolled in this study, regardless of the extent of surgical resection. Cases with a histologically positive surgical margin were defined as incomplete resection. Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived by the institutional review board in March 2010.

Patient Follow-Up

We examined the patients at 3-month intervals for the first 2 years and typically at 6-month intervals thereafter on an outpatient basis. The date and cause of death were verified by the medical records or, for the patients who died out of our surveillance, by follow-up inquiry letters sent to surviving families.

Clinicopathologic Information

We reviewed the medical records of each patient for clinicopathologic information, including age (dichotomized at

Table 1. Patient Characteristics

Characteristics	Patients (N = 504) N	%
Age		
Median, y (range)	65 (20–86)	
<65	243	48.2
≥65	261	51.8
Sex		
Male	262	52.0
Female	242	48.0
Smoking history		
Never	220	43.7
Ever	284	56.3
CEA (ng/mL)		
<5.0	327	64.9
≥5.0	177	35.1
Extent of resection		
Pneumonectomy	7	1.4
Lobectomy	450	89.3
Wedge resection or segmentectomy	47	9.3
Histologic differentiation		
Well	148	29.4
Moderately	282	56.0
Poorly	74	14.7
Pathologic stage		
IA/IB	261/107	51.8/21.2
IIA/IIB	42/22	8.3/4.4
IIIA/IIIB	68/4	13.5/0.8
T classification		
T1a/T1b	156/127	31.0/25.2
T2a/T2b	154/16	30.6/3.2
T3	48	9.5
T4	3	0.6
Nodal involvement		
N0	398	79.0
N1	42	8.3
N2	63	12.5
N3	1	0.2
Lymphatic permeation		
Ly (−)	411	81.5
Ly (+)	93	18.5
Vascular invasion		
V (−)	313	62.1
V (+)	191	37.9
Pleural invasion		
PL (−)	361	71.6
PL (+)	143	28.4
Histologic subtype		
BAC	29	5.8
Papillary	11	2.2
Acinar	3	0.6
Solid	12	2.4
Adenocarcinoma with mixed subtype	449	89.0
Predominant histologic subtype		
BAC	167	33.1
Papillary	190	37.7
Acinar	55	10.9
Solid	92	18.3

BAC = bronchioloalveolar carcinoma; CEA = preoperative serum carcinoembryonic antigen level.

the median age of 65), sex, smoking history (never- or ever-smoker), preoperative serum carcinoembryonic antigen level (cutoff at the normal upper limit of 5 ng/mL), extent of resection, histologic differentiation (well, moderately, or poorly differentiated), pathologic stage (as defined in the TNM Classification for Lung and Pleural Tumours of the Union Internationale Contre le Cancer, 7th edition [11]), pathologic T classification, pathologic nodal involvement, lymphatic permeation (present or absent), vascular invasion (present or absent), and pleural invasion (as defined in the TNM Classification, 7th edition [12, 13], present or absent).

Histologic Studies

All surgical specimens were fixed with 10% formalin and embedded in paraffin. The tumors were cut at approximately 5-mm intervals, and serial 4-μm sections were stained using the hematoxylin and eosin method. The Alcian blue–periodic acid Schiff method was used to visualize cytoplasmic mucin production, and the Victoria blue–van Gieson method was used to visualize elastic fibers. Blood and lymphatic vessels were identified by hematoxylin and eosin and Victoria blue–van Gieson staining. Vascular invasion and lymphatic permeation were histologically diagnosed by identifying cancer cells within blood and lymphatic vessels, respectively. Pleural invasion was eval-

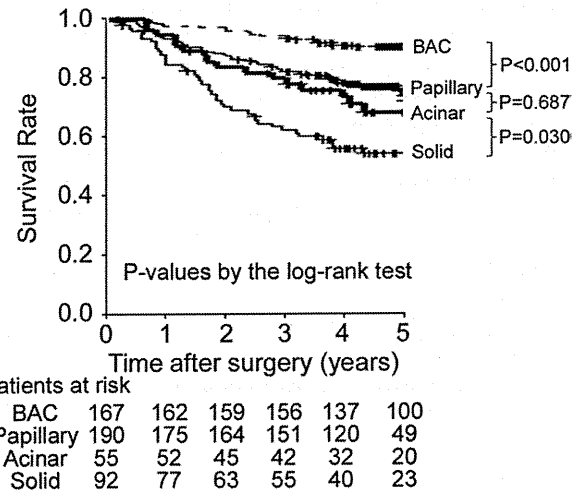

Fig 1. Overall survival curves according to predominant histologic subtype. (BAC = bronchioloalveolar carcinoma.)

Table 2. Solid Adenocarcinoma Component Ratio

Solid Adenocarcinoma Component (SAC)	N	%
(−)	294	58.3
(+)	210	41.7
Pure	12	2.4
Moderate (≥1/10)	132	26.2
Slight (<1/10)	66	13.1
Total	504	100

uated with the Victoria blue–van Gieson staining. Histologic diagnoses were based on the revised third edition of the World Health Organization Classification of Tumours [14]. According to this classification, we classified adenocarcinomas into five subtypes; BAC (nonmucinous or mucinous), acinar, papillary, solid adenocarcinoma, and mixed subtype. In this study, we defined SAC as cancer nests without any other subtype of structures (lepidic, acinar, or papillary growth), regardless of mucin production. We determined the predominant subtype, and in the tumors containing SAC, categorized the ratio of SAC into the following three groups; pure, moderate (1/10 or more, but not pure), and slight (less than 1/10). We chose 1/10 as the cutoff value based on a previous report on non-BAC component rates by Sakao and colleagues [4]. In pure SAC tumors, we confirmed mucin production by the Alcian blue–periodic acid Schiff method.

Statistical Analysis

Overall survival was defined as the time interval between the date of surgery and the date of death from any cause. The last follow-up observation was censored when the patient was alive or lost to follow-up. For univariate analyses, overall survival rates were estimated by the Kaplan-Meier method, and differences in survival among subgroups were compared using the log-rank test. Multivariate analyses were performed using the Cox proportional hazard model. Forward and backward stepwise procedures were performed to determine the combination of prognostic factors. The correlations between presence or absence of SAC and the clinicopathologic factors were evaluated by the χ^2 test. All probability values reported are two-sided, and the significance level was set at less than 0.05. The analyses were performed with SPSS 11.0 statistical software (Dr. SPSS II for Windows, standard version 11.0, SPSS Inc, Chicago, IL).

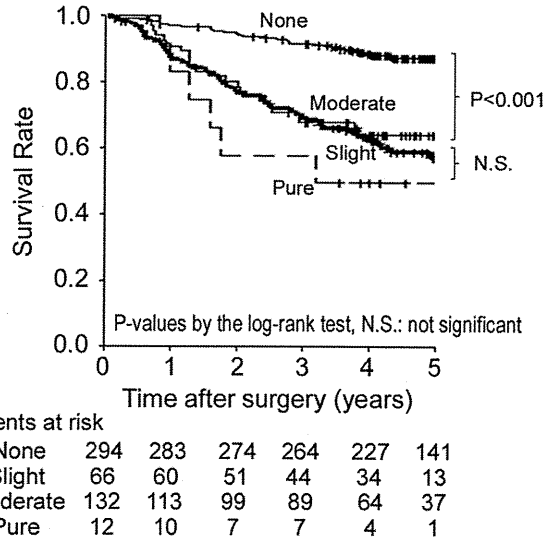

Fig 2. Overall survival curves according to amount of solid adenocarcinoma component. (N.S. = not significant.)

Results

Clinicopathologic Findings

The clinicopathologic characteristics of the 504 patients are summarized in Table 1. The median follow-up period was 4.8 years. There were slightly more men than women. The majority of the patients underwent lobectomy (including bilobectomy), and only slightly more than 1% underwent

Table 3. Relationship Between Solid Adenocarcinoma Component and Clinicopathologic Features

	SAC (N = 504)		
Variables	(−) (N = 294)	(+) (N = 210)	*p* Value[a]
Age (y)	Number of patients (%)		
<65	149 (61.3)	94 (38.7)	0.190
≥65	145 (55.6)	116 (44.4)	
Sex			
Male	127 (48.5)	135 (51.5)	<0.001
Female	167 (69.0)	75 (31.0)	
Smoking history			
Never	155 (70.5)	65 (29.5)	<0.001
Ever	139 (48.9)	145 (51.1)	
CEA (ng/mL)			
<5.0	213 (65.1)	114 (34.9)	<0.001
≥5.0	81 (45.8)	96 (54.2)	
T status			
T1	197 (69.6)	86 (30.4)	<0.001
T2–4	97 (43.9)	124 (56.1)	
Nodal involvement			
N (−)	264 (66.3)	134 (33.7)	<0.001
N (+)	30 (28.3)	76 (71.7)	
Lymphatic permeation			
Ly (−)	260 (63.3)	151 (36.7)	<0.001
Ly (+)	34 (36.6)	59 (63.4)	
Vascular invasion			
V (−)	229 (73.2)	84 (26.8)	<0.001
V (+)	65 (34.0)	126 (66.0)	
Pleural invasion			
PL (−)	241 (66.8)	120 (33.2)	<0.001
PL (+)	53 (37.1)	90 (62.9)	

[a] Pearson χ^2 test.

CEA = preoperative serum carcinoembryonic antigen level; SAC = solid adenocarcinoma component.

pneumonectomy. Adenocarcinoma with mixed subtype was present in approximately 90% of patients.

Relationship Between Predominant Histologic Subtype and Survival

Figure 1 shows survival curves stratified by predominant histologic subtype. Patients with BAC-predominant tumors had significantly better outcomes than those with non–BAC-predominant tumors. In contrast, patients with an SAC-predominant tumor showed significantly poorer prognosis than those with other tumor subtypes. There was no significant difference between patients with papillary subtype and those with acinar subtype. Their survival curves were between those for BAC and SAC subtypes.

Relationship Between Solid Adenocarcinoma Component Ratio and Survival

The distribution of SAC ratios is shown in Table 2. Pure solid adenocarcinoma was rare, accounting for only 5.7% of adenocarcinomas containing SAC and only 2.4% of the entire group of adenocarcinoma patients. The overall survival curves, stratified by SAC ratios, are shown in Figure 2. Although survival was significantly better in patients without SAC than in those with SAC, there were no statistically significant differences in survival among the three SAC ratio groups. Therefore, we examined all adenocarcinomas with SAC, regardless of SAC ratio, collectively as SAC+ adenocarcinoma in the following analyses.

Correlation Between Solid Adenocarcinoma Component and Clinicopathologic Features

The relationships between SAC and clinicopathologic features are shown in Table 3. Solid adenocarcinoma component significantly correlated with sex, smoking history, preoperative serum carcinoembryonic antigen level, pathologic T status, pathologic nodal involvement,

Table 4. Prognostic Significance for Overall Survival in all Patients

Characteristics	Number of Patients (Total = 504)	Overall 5-Year Survival Rate	Univariate Analysis *p* Value[a]	Multivariate Analysis	
				Hazard Ratio (% CI)	*p* Value[b]
Age (y)					
<65	243	81.4	<0.001	1.51 (1.04–2.20)	0.030
≥65	261	70.9			
Sex					
Male	262	65.7	<0.001	1.27 (0.72–2.21)	0.409
Female	242	86.8			
Smoking history					
Never	222	86.1	<0.001	1.51 (0.87–2.63)	0.143
Ever	282	67.6			
CEA (ng/mL)					
<5.0	327	83.1	<0.001	1.20 (0.82–1.74)	0.356
≥5.0	177	62.7			
T status					
T1	283	91.0	<0.001	2.03 (1.14–3.61)	0.016
T2–4	221	56.3			
Nodal involvement					
N (−)	398	87.4	<0.001	2.94 (1.95–4.44)	<0.001
N (+)	106	33.1			
Lymphatic permeation					
Ly (−)	411	83.4	<0.001	1.65 (1.12–2.42)	0.011
Ly (+)	93	43.5			
Vascular invasion					
V (−)	313	89.1	<0.001	1.70 (1.08–2.67)	0.023
V (+)	191	54.1			
Pleural invasion					
PL (−)	361	86.0	<0.001	1.29 (0.80–2.08)	0.296
PL (+)	143	50.5			
SAC					
SAC−	294	87.5	<0.001	1.63 (1.08–2.45)	0.020
SAC+	210	60.3			

[a] Log-rank test.

[b] Cox proportional hazard model.

CEA = preoperative serum carcinoembryonic antigen level; CI = confidence interval; SAC = solid adenocarcinoma component.

lymphatic permeation, vascular invasion, and pleural invasion.

Prognostic Significance of Solid Adenocarcinoma Component

Univariate analysis results from the log-rank test in all tumors are shown in Table 4. In the entire study cohort, significant differences in survival were observed according to the following factors: age, sex, smoking history, preoperative serum carcinoembryonic antigen level, pathologic T status, pathologic nodal involvement, lymphatic permeation, vascular invasion, pleural invasion, and SAC. Among these factors, multivariate analysis identified the following six independent prognostic factors: age, T status, pathologic nodal involvement, lymphatic permeation, vascular invasion, and SAC (Table 4).

When only stage I patients were evaluated by multivariate analysis, the following four independent prognostic factors were identified: sex, vascular invasion, pleural invasion, and SAC (Table 5).

Survival Differences According to Pathologic T Classification and Solid Adenocarcinoma Component

The overall survival curves stratified by pathologic T classification up to T2b and according to the amount of SAC are shown in Figure 3. The differences between T1a/SAC− (group A) and T1b/SAC− (group C), between T1b/SAC− (group C) and T1a/SAC+ (group B), between T1b/SAC− (group C) and T1a/SAC+ (group B), between T1b/SAC− (group C) and T2a/SAC− (group E), and between T2a/SAC− (group E) and T2a/SAC+ (group F) were statistically significant. In contrast, the differences in survival among T1a/SAC+ (group B), T1b/SAC+ (group D), and T2a/SAC− (group E) and between T2a/SAC+ (group F) and T2b/SAC− (group G) were not statistically significant. These findings suggest that the seven groups could be stratified into four categories in decreasing order of survival: (I) group A (T1a/SAC−); (II) group C (T1b/SAC−); (III) groups B (T1a/SAC+), D (T1b/SAC+), and E (T2a/SAC−); and (IV) groups F (T2a/SAC+) and G (T2b/SAC−). Although we compared the survival differences according to SAC among the groups from T2b to

Table 5. Prognostic Significance for Overall Survival in Stage I Patients

Characteristics	Number of Patients (Total = 368)	Overall 5-Year Survival Rate	Univariate Analysis *p* Value[a]	Multivariate Analysis	
				Hazard Ratio (95% CI)	*p* Value[b]
Age (y)					
<65	207	91.7	0.189		
≥65	161	87.3			
Sex					
Male	173	81.9	<0.001	2.71 (1.05–6.99)	0.039
Female	195	96.7			
Smoking history					
Never	184	96.0	<0.001	1.65 (0.67–4.05)	0.278
Ever	184	83.5			
CEA (ng/mL)					
<5.0	114	92.0	0.018	1.28 (0.64–2.57)	0.482
≥5.0	30	84.1			
T status					
T1	261	94.9	<0.001	1.39 (0.52–3.76)	0.515
T2	107	77.0			
Lymphatic permeation					
Ly (−)	339	91.6	<0.001	1.30 (0.61–2.80)	0.497
Ly (+)	29	68.5			
Vascular invasion					
V (−)	275	95.8	<0.001	2.90 (1.34–6.27)	0.007
V (+)	93	71.4			
Pleural invasion					
PL (−)	307	94.0	<0.001	2.65 (1.02–6.86)	0.045
PL (+)	61	68.3			
SAC					
SAC−	247	94.4	<0.001	2.30 (1.11–4.76)	0.024
SAC+	120	80.1			

[a] Log-rank test.

[b] Cox proportional hazard model.

CEA = preoperative serum carcinoembryonic antigen level; CI = confidence interval; SAC = solid adenocarcinoma component.

7 groups according to pT classification and SAC

group	T factor	SAC status	Patients (%)	Overall 5YSR* (%)
A	T1a	-	108 (24.4)	98.1
B	T1a	+	48(10.9)	78.6
C	T1b	-	89 (20.1)	94.1
D	T1b	+	38 (8.6)	78.7
E	T2a	-	69 (15.6)	79.7
F	T2a	+	85 (19.2)	52.7
G	T2b	-	5 (1.1)	50.0
total			442 (100)	

SAC, solid adenocarcinoma component, *: 5-year survival rate

P-values in survival difference

		P-value*
Group A vs	C	<0.001
Group C vs	B	0.011
	E	0.026
	D	0.021
	F	<0.001
Group B vs	E	0.643
	D	0.977
	F	0.001
	G	0.058
Group E vs	D	0.761
	F	<0.001
	G	0.018
Group D vs	F	0.005
	G	0.059
Group F vs	G	0.860

* : by log-rank test.

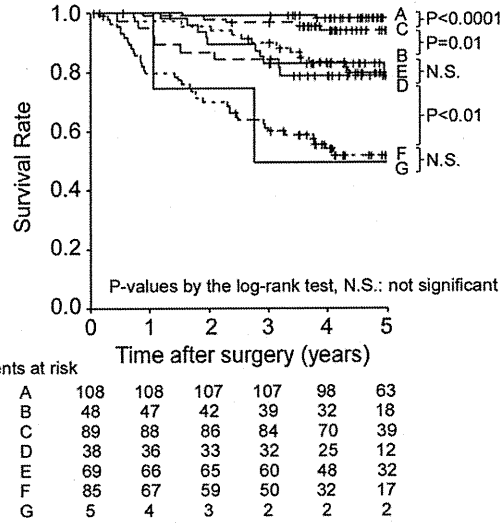

Fig 3. Overall survival curves according to pathologic T classification and solid adenocarcinoma component (SAC). (5YSR = 5-year survival rate; N.S. = not significant.)

T4 separately, there were no significant differences in these T classification groups (unpublished data).

Comment

Although solid adenocarcinoma is the most poorly differentiated subtype among the major histologic subtypes of pulmonary adenocarcinoma, only a few reports have attempted to evaluate the prognostic significance of SAC [9, 10]. When we analyzed surgically resected adenocarcinoma patients stratified by predominant subtype, patients with an SAC-predominant tumor had significantly poorer prognosis than those with other subtypes.

However, there have been no investigations on the impact of SAC ratio on prognosis. In our cohort, there were no statistical survival differences among the three SAC ratio groups. Patients with SAC had worse outcomes than those without, regardless of SAC ratio. Therefore, we examined all the patients with SAC collectively as SAC+ adenocarcinoma patients. Solid adenocarcinoma component was an independent prognostic factor in the entire cohort, and the prognostic effect was also observed when only stage I patients were analyzed. Although Riquet and associates [9] also reported that SAC+ adenocarcinoma patients demonstrated significantly worse outcomes compared with SAC− patients, they observed a statistically significant difference only in stage I patients.

Solid adenocarcinoma component correlated significantly with pathologic T classification, nodal involvement, vessel invasion, and pleural invasion. Riquet and colleagues [9] showed SAC correlation only with lymphatic permeation. Motoi and coworkers [15] reported that SAC-predominant tumors had significantly worse survival and were associated with gene clusters that were shown to be strongly correlated with heavy smoking history and larger tumor size. These findings suggest SAC is indicative of tumor invasiveness, proliferation, and dedifferentiation. Ding and colleagues [16] reported that mutations in *LRP1B*, *TP53*, and *INHBA* genes showed negative correlations with acinar, papillary, and BAC subtypes, but showed significant positive correlation with solid subtype in pulmonary adenocarcinomas. However, the biologic phenomena related to these gene mutations have not been identified. They also reported that *EGFR* mutation showed significant positive correlation with the papillary subtype, but not with the solid subtype. The tumor invasiveness observed in SAC+ tumors may thus be the result of specific gene abnormalities.

We evaluated the impact of SAC as an upstaging factor in T classification. The results suggested that otherwise T1 (T1a and T1b) adenocarcinomas with SAC need to be upstaged to T2a. Also, otherwise T2a adenocarcinomas with SAC need to be upstaged to T2b. In our study, SAC did not prove to be an upstaging factor for adenocarcinomas of otherwise T2b or higher. However, this may have been related to the small number of patients in these stages, and further investigation in a larger cohort is necessary.

Patients with adenocarcinoma in stage IB can benefit from uracil-tegafur adjuvant chemotherapy [17]. If SAC truly is an upstaging factor in T1 adenocarcinoma patients, otherwise stage IA patients with SAC may be upstaged to stage IB and benefit from uracil-tegafur adjuvant therapy. Therefore, pulmonary adenocarcinomas need to be carefully examined histologically for SAC, and data collected for future TNM classification revisions. Solid adenocarcinoma component responsiveness to chemotherapy also needs to be investigated to decide on the inclusion of adjuvant chemotherapy as the treatment of choice for stage IA SAC+ adenocarcinoma patients.

In conclusion, this study showed that pulmonary adenocarcinoma patients with SAC had poorer outcomes than those without, regardless of SAC ratio. The presence of SAC was an independent unfavorable prognostic factor, comparable to other pathologically invasive findings. Solid

adenocarcinoma component was an upstaging factor in the T classification for T1 and T2a pulmonary adenocarcinomas. If SAC is present, we propose that T1 and T2a tumors should be classified as T2a and T2b, respectively.

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INVITED COMMENTARY

From their analyses of 504 patients who underwent resection of lung adenocarcinoma and whose tumors were well characterized histologically, Ohtaki and colleagues [1] suggest that the presence of the solid adenocarcinoma subtype is an independent adverse prognostic factor that should be considered in future revisions of the lung cancer staging system.

During the past few years, it has become increasingly evident that lung adenocarcinoma is a heterogeneous disease and that the histologic subtypes of adenocarcinoma are associated with distinct molecular features and clinical behaviors. For instance, *EGFR* mutations occur most frequently in nonsmokers or former light smokers, are associated with papillary, micropapillary, and lepidic-predominant (bronchioloalveolar) adenocarcinomas, predict sensitivity to tyrosine kinase inhibitor therapy and a better prognosis after surgical resection. By contrast, solid and mucinous adenocarcinoma subtypes often occur in patients with a significant smoking history, are reported to be associated with *KRAS* mutations, and are associated with a more aggressive clinical behavior.

However, efforts to correlate radiologic, pathologic, and molecular features of lung adenocarcinomas with clinical outcomes are relatively recent and still very incomplete. Many molecular abnormalities that may explain the behavior of lung adenocarcinoma subtypes remain undefined. In the future, such correlations will likely allow the optimal selection of patients for multimodality therapy and may influence the use of limited resections for patients with very early-stage lung adenocarcinoma. They will also facilitate the development of molecularly targeted therapies.

Growing recognition of the importance of the links between lung adenocarcinoma subtypes and biologic and clinical characteristics recently led to an international multidisciplinary effort to revise the pathologic classification of lung adenocarcinoma in ways that recognize these links [2]. Although not definitive enough to influence future revisions of the staging system, the work of Ohtaki and colleagues contributes in an important way to the growing body of literature on this topic [3]. Additional molecular and clinical studies in this area are needed to support or refine the new proposed histologic classification and to inform future revisions of the lung

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Influence of Cigarette Smoking on Histological Subtypes of Stage I Lung Adenocarcinoma

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Background: The purpose of this study was to examine the association between cigarette smoking and histological subtypes of lung adenocarcinoma.

Methods: We reviewed a total of 320 consecutive patients with stage I adenocarcinoma who underwent complete resections with systematic node dissections from January 2004 to December 2006 at the National Cancer Center Hospital East.

Results: A statistically significant difference was observed in recurrence-free probabilities between never smokers and ever smokers (3-year recurrence-free probabilities of 95.6% and 88.6%, respectively, $p = 0.034$). Among adenocarcinoma histological subtypes, only a solid component was significantly more frequent in ever smokers than in never smokers ($p < 0.001$). Among patients with solid components, significantly more cases had lymphatic permeation ($p = 0.007$), intratumoral vascular invasion ($p < 0.001$), and visceral pleural invasion ($p < 0.001$). Multivariate analysis revealed that ever-smoking history was the only statistically significant independent clinical predictor for a solid component ($p < 0.001$). Among ever smokers, smoking extent in pack-years of patients with solid components was significantly greater than that of those without solid components ($p < 0.001$). With respect to predominant subtypes, smoking extent in pack-years of patients with predominantly solid adenocarcinomas was significantly greater than that of patients with predominantly bronchioloalveolar carcinoma, papillary, or acinar adenocarcinomas (all $p < 0.001$).

Conclusion: A greater smoking extent was associated with the presence of adenocarcinoma solid components, which may have more aggressive biological features resulting in poorer outcomes.

Key Words: Lung cancer, Adenocarcinoma, Subtype, Thoracic surgery, Cigarette smoking, Solid component.

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Adenocarcinoma of the lung is the most frequent histological subtype of lung cancer, and its incidence is increasing in most countries.[1] In Japan, adenocarcinoma is also the most common histological subtype of resected lung cancers, accounting for more than 60% of cases.[2]

Adenocarcinomas are typically very heterogeneous, showing a wide variety of histological features, including bronchioloalveolar carcinoma (BAC), acinar, papillary, and solid adenocarcinoma.[3] Among these major histological subtypes, BAC is often reported to be associated with a favorable prognosis,[4–6] whereas the other subtypes are considered invasive components and are associated with poor outcomes, particularly solid components.[7,8]

Smoking is a well-known causative factor of lung cancer[9] and is associated with all the histological subtypes of lung cancer.[10–12] Although the association of cigarette smoking with adenocarcinoma is reported to be the weakest,[12] its association with carcinogenesis of lung adenocarcinoma is established. Several studies have recently reported that ever smokers had significantly unfavorable prognoses compared with never smokers among patients with lung adenocarcinoma.[13,14] Because the association between smoking and postoperative complications is well known,[13,15] this factor may partially contribute to unfavorable cancer survivals of ever smokers. Another possible reason is that the number of patients with BAC subtypes among never smokers has recently increased,[16] which may also partially contribute to the favorable prognoses among never smokers.

Although many studies have reported on the associations between cigarette smoking and lung adenocarcinomas,[13,14] several questions regarding the influence of cigarette smoking on lung adenocarcinomas remain unanswered. Primarily, whether cigarette smoking affects the biological behaviors of lung adenocarcinomas, especially histological subtypes of adenocarcinoma? If so, with which subtype(s) is cigarette smoking associated? To answer these questions, we reviewed a series of consecutive patients with pathological stage I adenocarcinomas who underwent complete resections in our hospital. The main purpose of this study was to investigate the association between cigarette smoking and the histological subtypes of adenocarcinoma.

PATIENTS AND METHODS

Patients Selection

A total of 466 consecutive patients with clinical stage I adenocarcinoma underwent operation from January 2004 to

December 2006 at the National Cancer Center Hospital East. We excluded three patients from our study because they had received preoperative chemotherapy, radiation therapy, or both. Among the 463 patients, 458 patients underwent complete surgical resection. The operative findings and pathological examination of surgical specimens revealed that 90 patients were reclassified as pathological stage II or higher and were up-staged. Among the 368 patients diagnosed as pathological stage I, 48 patients underwent limited surgery. The remaining 320 patients with pathological stage I adenocarcinoma who underwent complete tumor resection with lobectomy or a more extensive surgery along with systematic lymph node dissection were enrolled as the subjects of this study.

Pathological Evaluations

Disease stages were diagnosed based on the TNM classification of the International Union Against Cancer, 7th edition.[17] The histological type was determined according to the World Health Organization's classification.[3] Intratumoral vascular invasion (IVI) and visceral pleural invasion (VPI) were evaluated by staining with hematoxylin-eosin and Victoria blue-van Gieson stains. VPI was classified according to the TNM classification, 7th edition.[17] Adenocarcinoma histological subtypes were categorized into BAC (nonmucinous or mucinous), papillary, acinar, and solid adenocarcinomas according to the World Health Organization's classification.[3] Mucin production in a solid adenocarcinoma component was confirmed by the alcian blue-periodic acid Schiff method. We determined the predominant subtype, and each component was defined as present if observed in more than 1 of 10 of a tumor; otherwise, it was defined as absent.

Clinicopathological Information

We prospectively collected information on cigarette smoking status using outpatient clinic questionnaires, which were answered by patients on their first clinic visit. Patients were asked to record the age when they started smoking, duration of smoking, and average daily cigarette consumption. No environmental cigarette smoke exposure data were collected. The extent of smoking was quantified in pack-years (PY), with 1 PY equivalent to 20 cigarettes, on average, per day for 1 year. Before admission, all patients were required to stop smoking.

We reviewed the medical records of each patient for clinicopathological information. This included age (dichotomized at the median age of 65 years), gender, smoking history (never- or ever smoker), smoking extent in PY, forced expiratory volume in 1 second % ($<70\%$ or $\geq 70\%$), preoperative serum carcinoembryonic antigen (CEA) level (cutoff at the normal upper limit of 5 ng/ml), tumor laterality (right or left), primary lobe (upper, middle, or lower lobe), tumor size (≤ 3 cm or >3 cm), BAC component (present or absent), papillary component (present or absent), acinar component (present or absent), solid component (present or absent), predominant histological subtypes (BAC, papillary, acinar, or solid), lymphatic permeation (present or absent), IVI (present or absent), and VPI (as defined in the TNM classification, 7th edition,[17] present or absent).

Statistical Analysis

Differences in categorical outcomes were evaluated by χ^2 test. Continuous variables were compared using t tests. To offset the prognostic impact of comorbidities associated with cigarette smoking, we investigated recurrence-free probabilities for this study. The length of recurrence-free probability was calculated in months from the date of resection to the date of first recurrence or last follow-up. To calculate the recurrence-free probability, patients who died without recurrence or who were known to be recurrence free at the date of last contact were excluded from the calculation. For univariate analyses, all recurrence-free probabilities were estimated using the Kaplan–Meier method, and comparisons of these variables were made using the log-rank test. Multivariate analyses were performed using Cox's proportional hazard regression model. Clinical predictors for the presence of a solid component were evaluated by logistic regression analyses. The predictors from univariate analyses were also evaluated using multiple regression analyses. The p value less than 0.2 in a univariate model was set as the threshold used for selection of variables in a multivariate model. All reported p values were two sided, and the significance level was set at less than 0.05. Analyses were performed using SPSS version 11.0 (Dr. SPSS II for Windows, standard version 11.0, SPSS Inc., Chicago, IL) and GraphPad Prism (Prism for Windows, Version 5.02, GraphPad Software, Inc., La Jolla, CA).

Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived by the institutional review board in April 2010.

RESULTS

Patient Characteristics and Recurrence-Free Probabilities According to Clinicopathological Factors

The median follow-up period was 37 months (range: 3–60 months). Recurrence-free probabilities according to clinicopathological factors are presented in Table 1. Univariate analysis (log-rank test) identified eight significant risk factors for recurrence: gender, smoking history, preoperative serum CEA level, tumor diameter, the presence of solid component, lymphatic permeation, IVI, and VPI (Table 1).

A statistically significant difference was observed in recurrence-free probabilities between never smokers and ever smokers: 3-year recurrence-free probabilities of 95.6% and 88.6%, respectively (Figure 1). Figures 2*A–D* show the recurrence-free probability curves according to the histological subtypes. No statistically significant differences were present in the recurrence-free probabilities between patients with and without BAC (3-year recurrence-free probabilities of 90.2% and 92.9%, respectively; $p = 0.522$; Figure 2*A*), with and without papillary (88.8% and 93.2%, respectively; $p = 0.539$; Figure 2*B*), and with and without acinar (95.2% and 88.9%, respectively; $p = 0.092$; Figure 2*C*) components. In contrast, the 3-year recurrence-free probability for patients with solid components (84.9%) was significantly lower than that for those without solid components (96.3%; $p = 0.001$; Figure 2*D*).

TABLE 1. Patient Characteristics, and Recurrence-Free Probabilities According to Clinicopathological Factors

Characteristics	No. of Patients (%)	Recurrence-Free Probability 3-year (%)	Univariate *p* Value†	Multivariate Analysis HR	95% CI	*P*-Value
Total	320	92.2				
Clinical factors						
Age (years)						
≤65	169 (53)	93.5	0.534	Not included multivariable model		
>65	151 (47)	90.5				
Gender						
Women	175 (55)	95.8	0.009*	1		
Men	145 (45)	87.4		1.282	0.330–4.986	0.72
Smoking history						
Never-smoker	148 (46)	95.6	0.034*	1		
Ever-smoker	172 (54)	88.6		1.644	0.354–7.629	0.525
CEA						
Within normal range	148 (46)	94.9	0.007*	1		
Elevated	172 (54)	85		1.221	0.499–2.989	0.661
FEV1 %						
≥70	277 (87)	92.8	0.591	Not included multivariable model		
<70	42 (13)	87.9				
Tumor laterality						
Right	206 (64)	93.5	0.499	Not included multivariable model		
Left	114 (36)	90				
Primary lobe						
Upper or middle lobe	227 (71)	93.3	0.297	Not included multivariable model		
Lower lobe	93 (29)	89.4				
Tumor size (cm)						
≤3.0	253 (79)	96.4	0.015*	1		
>3.0	67 (21)	89.5		1.165	0.393–3.457	0.783
Histological subtypes						
BAC component						
Absent	95 (30)	90.2	0.522	Not included multivariable model		
Present	225 (70)	92.9				
Papillary component						
Absent	83 (26)	88.8	0.539	Not included multivariable model		
Present	237 (74)	93.2				
Acinar component						
Absent	163 (51)	95.2	0.092	1		
Present	157 (49)	88.9		1.151	0.474–2.797	0.756
Solid component						
Absent	199 (62)	96.3	0.001*	1		
Present	121 (38)	84.9		1.59	0.661–3.823	0.301
Pathological factors						
Lymphatic permeation						
Absent	297 (93)	94.8	<0.001*	1		
Present	23 (7)	58.4		2.698	1.050–6.932	0.039*
Intratumoral vascular invasion						
Absent	245 (77)	98.6	<0.001*	1		
Present	75 (23)	70.9		14.65	3.804–56.422	<0.001*
Visceral pleural invasion						
Absent	261 (82)	95.5	<0.001*	1		
Present	59 (18)	77.9		1.006	0.393–2.581	0.989
Gene mutation status						
EGFR						
Wild type	71 (22)	87.7	0.783	Not included multivariable model		
Mutated	12 (4)	90				
Not examined	237					

*, significance; Numbers in parentheses, percentages; †, log-rank test; HR, hazard ratio; CI, confidence interval; CEA, preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL; FEV1%, forced expiratory volume % in one second; BAC, bronchioloalveolar carcinoma; EGFR, epidermal growth factor receptor.

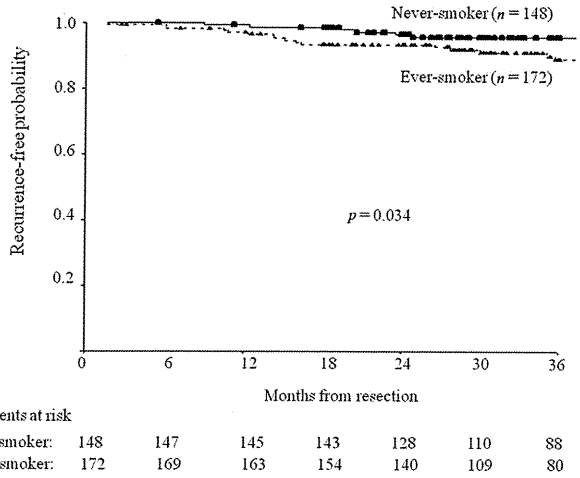

FIGURE 1. Recurrence-free probability curves according to smoking history in the entire cohort.

On multivariate analysis using the Cox regression model, presence of lymphatic permeation and presence of IVI remained statistically significant independent predictors for postoperative recurrence after resection (Table 1).

Univariate and Multivariate Analyses of Clinical Predictors for the Presence of a Solid Component

Because of the significantly lower recurrence-free probability only for patients with solid components among adenocarcinoma histological subtypes, we examined clinical predictors for the presence of a solid component. Univariate analyses revealed three significant clinical predictors for the presence of a solid component: gender, smoking history, and CEA (Table 2). On multivariate analysis, ever-smoking history was the only statistically significant independent clinical predictor for the presence of a solid component ($p < 0.001$; Table 2).

Associations between Solid Components and Other Pathological Factors

To clarify the reasons why patients with solid components had the significantly lower recurrence-free probability compared with those without solid components, we examined

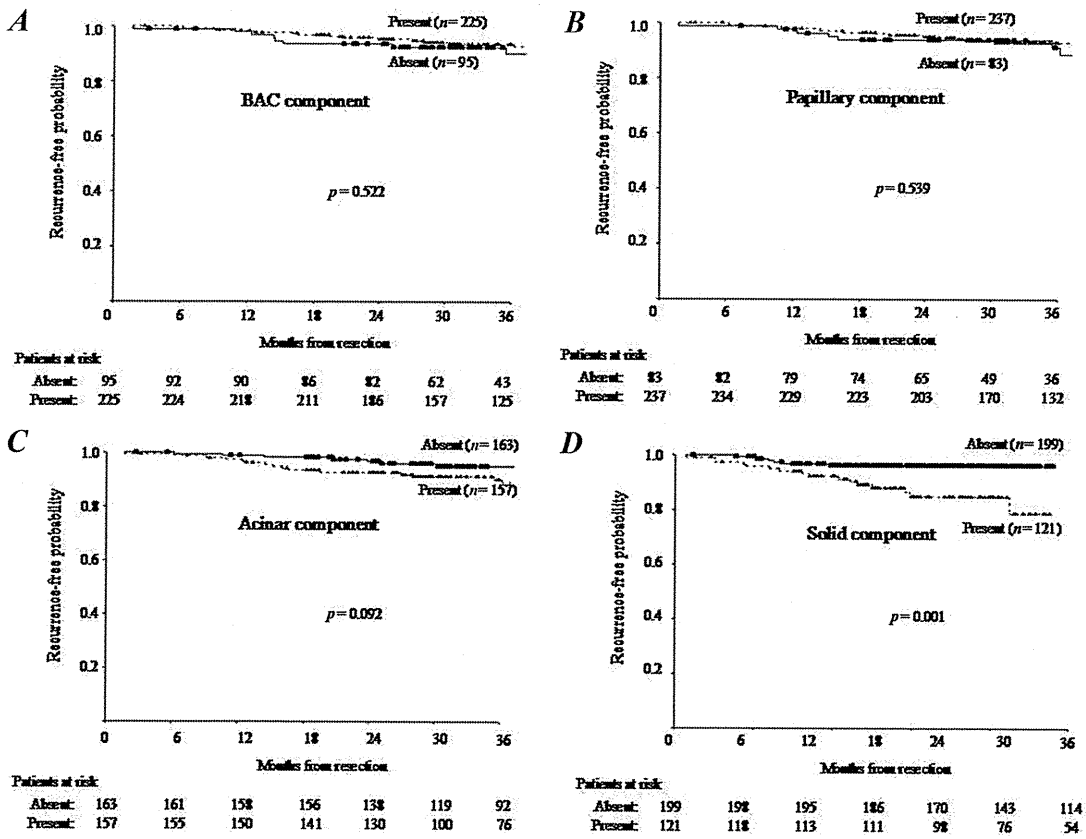

FIGURE 2. Recurrence-free probability curves according to the histological subtypes in the entire cohort. *A*, Recurrence-free probability curves of patients with and without bronchioloalveolar carcinoma (BAC) components. *B*, Recurrence-free probability curves of patients with and without papillary components. *C*, Recurrence-free probability curves of patients with and without acinar components. *D*, Recurrence-free probability curves of patients with and without solid components.

TABLE 2. Univariate and Multivariate Analyses of Predictors for the Presence of a Solid Component

	Univariate Analysis			Multivariate Analysis		
Variables	**HR**	**95% CI**	p^a	**HR**	**95% CI**	p^b
Age (yr)						
>65	1.37	0.871–2.156	0.173	1.423	0.859–2.359	0.642
≤65	1			1		
Gender						
Male	3.182	1.988–5.092	<0.001[c]	1.543	0.852–2.795	0.152
Female	1			1		
Smoking habits						
Ever smoker	4.419	2.680–7.287	<0.001[c]	3.319	1.779–6.191	<0.001[c]
Never smoker	1			1		
CEA						
Elevated	2.103	1.222–3.316	<0.001[c]	1.517	0.872–2.639	0.14
Within normal range	1			1		
FEV_1%						
<70	1.798	0.936–3.454	0.078	1.032	0.495–2.155	0.933
≥70	1			1		
Tumor laterality						
Right	1.182	0.739–1.890	0.486	Not included in multivariable model		
Left	1					
Primary lobe						
Upper or middle lobe	1.079	0.654–1.776	0.767	Not included in multivariable model		
Lower lobe	1					
Tumor size (cm)						
>3.0	1.443	0.836–2.491	0.187	1.156	0.629–2.124	0.742
≤3.0	1			1		

[a] Logistic regression procedure.
[b] Multiple regression analysis.
[c] Significance.
CEA, preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/ml; FEV_1%, forced expiratory volume % in 1 second; HR, hazard ratio; CI, confidence interval.

associations between solid components and pathological factors including statistically significant independent predictors for recurrence such as lymphatic permeation and IVI (Table 3). Among patients with solid components, significantly more cases were found with lymphatic permeation ($p = 0.007$), IVI ($p < 0.001$), and VPI ($p < 0.001$). In addition, significantly more cases with epidermal growth factor receptor (EGFR) mutations were found in patients without solid components ($p = 0.033$).

Associations between Smoking History or Smoking Extent and Adenocarcinoma Histological Subtypes

The presence of a solid component was strongly associated with cigarette smoking (Table 2). Further evaluations were performed for elucidating the association between cigarette smoking and histological subtypes other than solid components in addition to other pathological factors (Table 4).

A BAC or papillary component was significantly more frequent in never smokers than in ever smokers ($p < 0.001$ and $p = 0.01$, respectively; Table 4). Among ever smokers, significantly more cases were found with IVI ($p = 0.025$). In addition, significantly more cases with EGFR mutations were found in never smokers ($p = 0.001$).

Figures 3*A–D* show the associations between smoking extent and histological subtypes for ever smokers only. In ever smokers only, the smoking extent in PY of patients with BAC components (mean = 25.0 ± 2.5) was significantly lower than that of those without BAC components (mean = 44.9 ± 3.8; Figure 3*A*). In contrast, the smoking extent in PY of patients with solid components (mean = 45.2 ± 3.2) was significantly greater than for those without solid components (mean = 30.0 ± 2.7; $p < 0.001$; Figure 3*D*).

Figure 4 shows the smoking extent in PY of all patients stratified by their predominant histological subtypes. The smoking extent in PY of patients with predominantly solid adenocarcinomas (PY = 45.5 ± 4.5) was significantly greater than that of those with predominantly BAC (PY = 14.5 ± 2.2), papillary (PY = 16.6 ± 2.4), or acinar (PY = 23.5 ± 4.7) adenocarcinomas (all $p < 0.001$).

Figure 5 shows the association between smoking extent and the proportions of tumors with solid components in the entire study cohort. Patients with higher proportions of solid tumor components also had greater smoking extent in PY. The smoking extent in PY of patients who had tumors with more than 50% solid components was greater than that of patients who had tumors with 10 to 50% solid components